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Bone Marrow Failure and Myelofibrosis in a Case of PVP Storage Disease

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''PVP storage disease'' is a disorder occurring in patients who have received high molecular weight polyvinylpyrrolidone (PVP), which cannot be excreted from the body. These large polymers deposit in the histiocytes and cause proliferation and infiltration of histiocytes in the reticuloendothelial system. There was usually no significant damage to these organs except that prolonged administration might cause bone destruction, skin lesions, arthritis, and polyneuropathy. We describe a patient who had received a large amount of PVP-containing solution for years. Severe bone marrow failure with extensive infiltration of bone marrow by foamy histiocytes occurred later. In addition, she suffered from multiple pathological fractures with spinal cord compression and arthritis of bilateral knee joints. Am. J. Hematol. 57:68–71, 1998.

Key words: polyvinylpyrrolidone; myelofibrosis; pathologic fracture

INTRODUCTION

Polyvinylpyrrolidone (PVP) is a polymer of the monomer N-vinylpyrrolidone. It had been used as a plasma expander, or a retarding agent for subcutaneous injection of hormone preparation such as vasopressin [1–6]. High molecular weight PVP can not be eliminated from the kidneys, thus PVP is retained in the reticuloendothelial system (RES). The name ''PVP storage disease'' is applied to this disease [1–9]. Despite extensive histiocytic accumulation in tissues, no major organ damage had been reported initially [1,2,4–6]. Most damages result from bone destruction, polyneuropathy, arthritis, or granulomatous lesions in the skin [3,4,6–8]. In Taiwan, PVP is prevalent as a plasma expander and several reports have discussed this issue [8–10]. Herein, we describe a patient who had received long-term parenteral administration of a large amount of PVP and in whom heavy infiltration of bone marrow with abnormal histiocytes and bone marrow failure developed. In reviewing the English literature, there are no reports regarding the adverse effect of PVP on the bone marrow.

CASE REPORT

A 39-year-old Taiwanese female was in good health in the past. Since 1990, she received PVP-containing intravenous solution for nutritional support, which was prescribed by an illegal doctor. Totally, more than 50 bottles (500 ml/bottle, 5% PVP) had been administered. In May 1991, she began to suffer severe generalized bone pain. On examination, she was pale and there was no lymphadenopathy, hepatosplenomegaly, or skin lesions. The extremities and joints were normal. Hemogram showed: Hb 7.0 g/dL, WBC 1.9×10^9/L (myelocytes 2%, bands 2%, segmented neutrophils 49%, lymphocytes 40%, monocytes 7%, and normoblasts 2/100 WBC) and platelet count 130×10^9/L. Biochemical studies were normal. LDH was 59 IU/L (normal 47–140 IU/L). X-ray of chest, shoulder, and pelvis was normal. Bone scan revealed active bilateral hip lesions. Bone marrow aspiration re-

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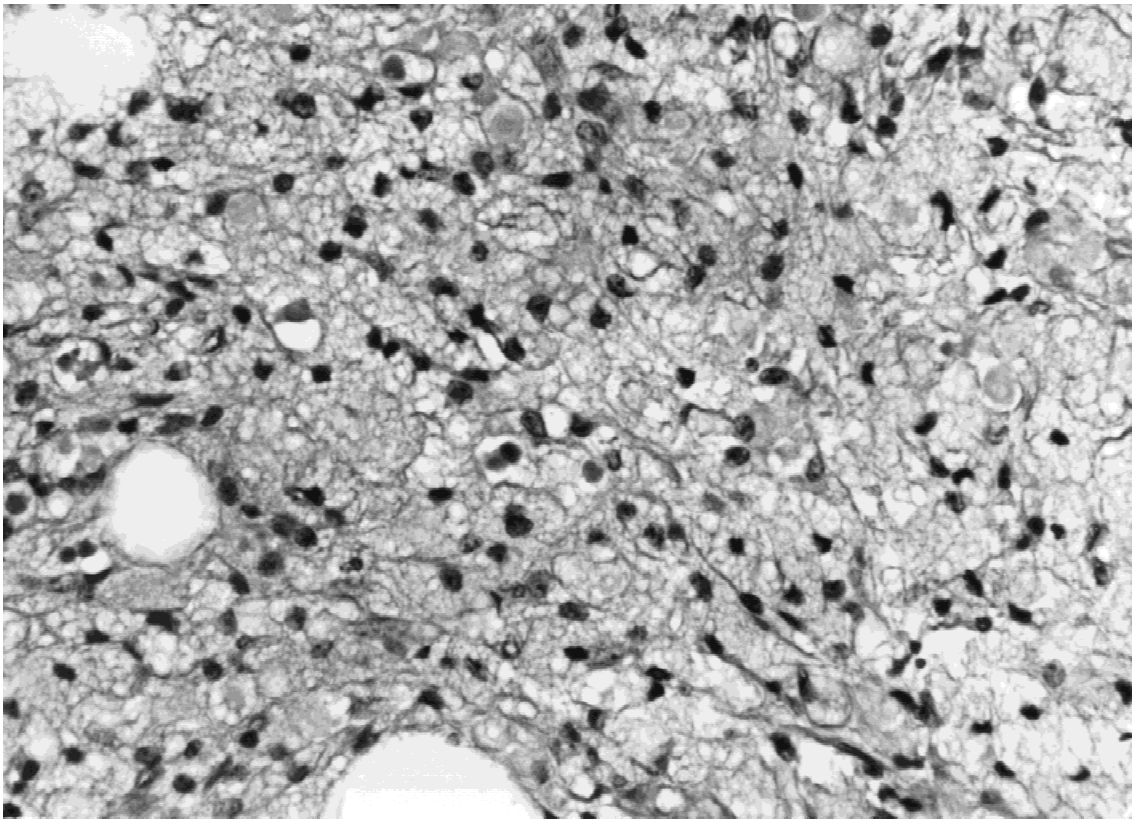

Fig. 1. Bone marrow biopsy showing diffuse infiltration by foamy histiocytes (×200).

sulted in a dry tap and the bone marrow biopsy showed diffuse foamy histiocytic infiltration, which replaced almost all the marrow spaces. The histiocytes contained many vacuoles and amorphous basophilic inclusions (Fig. 1). Reticulin stain of the marrow biopsy revealed the reticulin fibers were markedly increased and coppered to encircle every individual macrophage (Fig. 2). ''PVP storage disease'' was diagnosed. Eleven months later, severe lumbago with limited range of motion of vertebral spine developed. Neurologic examination showed the cranial and peripheral nerves were normal. Muscle strength of bilateral lower extremities was decreased. X-ray studies of lumbar spine showed compression fracture of T11 and T12 and radiolucencies in bodies of L4 and L5. Bone scan demonstrated multiple active bone lesions involving thoraco-lumbar spines, greater trochanter of left femur, right 6th rib, and medial third portion of right clavicle. Hemogram revealed Hb 6.4 gm%, WBC 1.6×10^9/L (myelocytes 1%, bands 2%, segmented neutrophils 48%, basophils 1%, monocytes 9%, lymphocytes 39%, normoblasts 3/100 WBC), and platelet count 26×10^9/L. CT scan of abdomen showed hepatosplenomegaly. Two months afterward, she became completely bedridden with urine and stool incontinence. Myelogram showed multiple compression fracture of T9, 11, 12, and L3-5, and central impression to the thecal sac over T11, T12, L4, and L5. A subcutaneous nodule was palpated over left thigh and aspiration from the nodule showed predominantly histiocytes. The skin had normal appearance but the histology of skin revealed many perivascular infiltrations of vacuolated blue histiocytes in the dermis and subcutaneous tissue. The abnormal histiocytes in the skin and bone marrow showed positive reaction to mucicarmine, colloidal iron, and alkaline Congo red. PAS stain was negative. Immunohistochemical study of these cells using monoclonal antibody KP1 (CD68) revealed positive reaction. In addition, she suffered bilateral knee joint swelling and pain. Synovial fluid studies showed many foamy histiocytes scattered and few neutrophils and lymphocytes. Five years after the initial presentation, there was no sign of recovery despite discontinuation of PVP-containing fluid infusion.

DISCUSSION

PVP has been used as a plasma expander since World War II, and many studies had reported its metabolism and clinical effect later [1,2,4]. For low molecular weight PVP, it can be eliminated through the kidneys and there is no clinical significance. In contrast, high molecular weight PVP accumulates in the body, usually in the reticuloendothelial system including lymph nodes, liver,

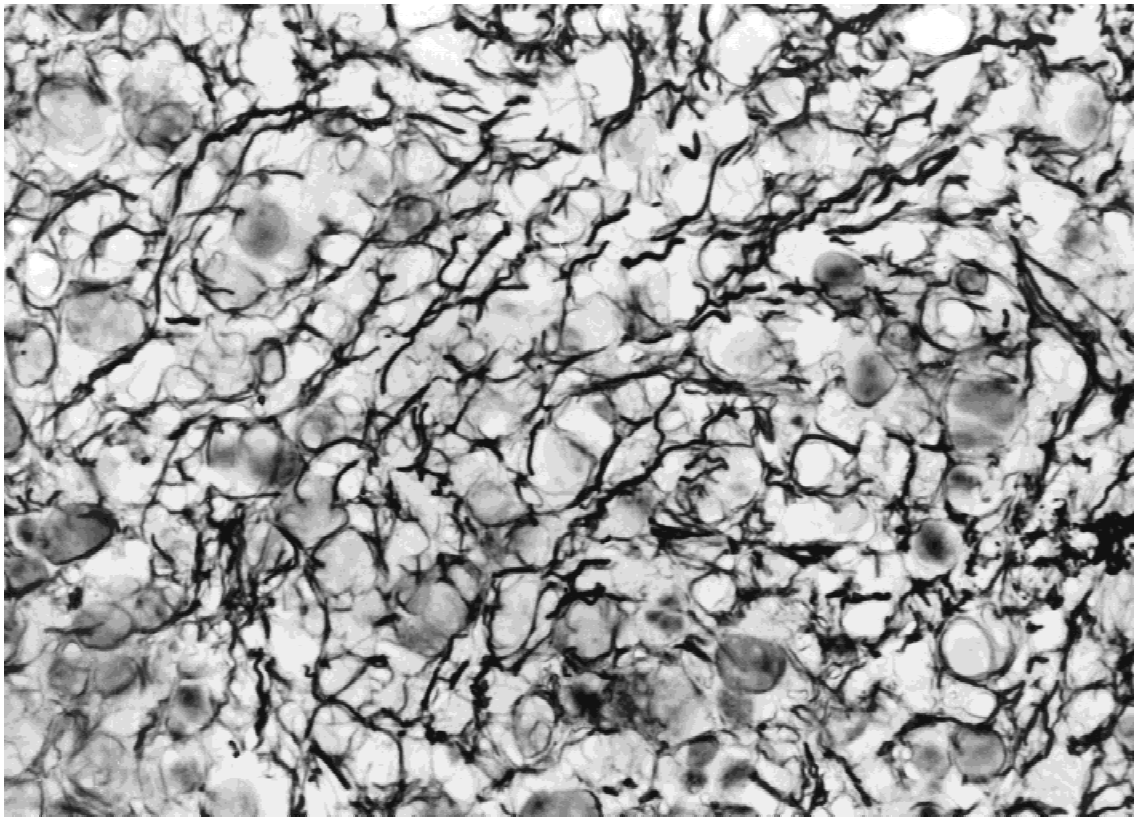

Fig. 2. Marked increase in reticulin fibers with reticulin stain.

spleen, and bone marrow [1–7]. Mesenchymal tissues containing macrophages may have these abnormal histiocytes infiltrating, such as skin, muscles, and connective tissues [3,4,9]. In addition, osteocytes and some malignant cells with characteristics of mesenchymal cells may have PVP deposit in the cytoplasm [8,10]. Most cases were reported as an incidental finding during the examination of surgical specimens [5–7,9,10]. The retained polymers in the histiocytes created a characteristic finding showing histiocytes with basophilic cytoplasm and variable-sized vacuoles [1–9]. Cytochemical studies of these histiocytes revealed positive reaction to Congo red and mucicarmine stain [3,7–10]. Because the abnormal histiocytes contained vacuoles like mucoid substance mimicking signet-ring cells, a misdiagnosis of malignancy might be made [9]. Initially, in spite of storage of high-molecular PVP, there are no disturbances in function in the organs concerned [2,4,5]. Later, bone destruction, arthritis, and polyneuropathy were reported [3,6–8]. Skin lesions were noted sometimes, especially when the patients received subcutaneous injection of fluid containing PVP. The lesions include papules, nodules, and patches [3,4]. Pathologic fracture was a significant sequalae of PVP storage disease; involvement of femur, humurus, and tibia had been observed [3,7,8]. Kepes et al. had reported that PVP deposited in osteocytes induced ''mucoid degeneration'' and softening of bones that resulted in pathologic fracture [8]. In regard to bone marrow involvement of PVP, most reports described only infiltration of foamy histiocytes in the bone marrow and no inflammation or fibrosis in relation to the storage was found. There were no significant hematological effects [3,5–7]. Myelofibrosis is associated with many diseases, including hematologic and nonhematologic malignancies, infection, toxic substance, and some rare endocrine diseases [11]. This patient presented with severe anemia, and bone marrow biopsy showed myelofibrosis and heavy infiltration of histiocytes. There was no huge splenomegaly and no tear-drop RBC were found in the peripheral blood smear. Therefore, primary myelofibrosis is not likely. No malignancy or systemic infection could be found at diagnosis or during follow-up. Among the toxic substances, benzene is well known for its myelotoxicity; myelofibrosis induced by benzene has been documented [12]. In this report, we present an additional chemical agent that might induce myelofibrosis and bone marrow failure.

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